Please add new claims 43-45 to read as follows:

43. (New) A transgenic non-human mammal whose cells express a *Fkh*^{sf} transgene comprising a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:1, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal, and wherein the mammal is a mouse, rat, rabbit, sheep, goat, or pig.

44. (New) A transgenic mouse whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule selected from the group consisting of (i) a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:4 and (ii) a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:3, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mouse.

45. (New) A transgenic non-human mammal whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule selected from the group consisting of (i) a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:4 and (ii) a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:3, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal, and wherein the mammal is a mouse, rat, rabbit, sheep, goat, or pig.

REMARKS

Reconsideration of the present Application in view of the above amendments and the following remarks is respectfully requested. Claims 34-42 are currently pending. Claims 34-42 have been amended and new claims 43-45 have been added to more clearly define the subject matter encompassed by Applicants' invention. Support for the amended and new claims may be found in the specification, for example, at page 11, lines 11-30; page 20, lines 4-9; page 22, lines 10-12; page 33, lines 3-7; page 34, lines 24-29; page 37, line 15 through page 38, line 5; SEQ ID

NOs:1-4. Claims 36 and 41-42 stand objected to for being dependent upon a rejected base claim but would be allowable if rewritten in independent form including all limitations of the base claim. Applicants respectfully submit that the amendments submitted herewith have placed the claims in condition for allowance. Claim 42 was also amended without limitation to distinctly claim and particularly point out what Applicants regard as their invention. Support for the amendment may be found in the specification, for example, at page 22, lines 10-12 and page 37, lines 19-20; and page 37, line 28 through page 38, line 5. The specification has been amended solely to correct typographical errors in the length of the nucleotide sequence depicted in Figure 3, and the nucleotide positions that initiate and terminate the coding region. Support for the amendment may be found in the specification, for example, at page 34, lines 24-29, and in SEQ ID NO:3. No new subject matter has been added.

The Examiner requested that a clean copy of all pending claims be included with this Response, and Applicants have enclosed same. Also, attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version With Markings to Show Changes Made**."

REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH (ENABLEMENT)

The PTO rejects claims 34-35 and 37-39 under 35 U.S.C. § 112, first paragraph, asserting lack of enablement. Specifically, the Action asserts that the scope of the claims is not commensurate with the subject matter enabled by the disclosure. The Action concedes that the specification is enabling for a transgenic scurfy mouse whose cells express a transgene that contains a sequence encoding a mouse Fkh^{sf} protein, wherein the expression of an *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mouse. The Action asserts, however, that the specification does not reasonably provide enablement for any and all transgenic non-human mammals whose cells express a transgene that contains a *Fkh*^{sf} coding sequence obtained from any animal. The PTO also rejects claims 35 and 37-39 on the grounds that the claims fail to recite the required phenotype that would provide enabling guidance to a skilled artisan to use the claimed transgenic mouse.

Applicants respectfully traverse these grounds for rejection and submit that as disclosed in the specification and recited in the instant claims, the claimed invention was fully

enabled at the time the Application was filed. Applicants' invention is directed in pertinent part to a transgenic mouse whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mouse. In certain embodiments, the *Fkh*^{sf} transgene comprises a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:1. In certain other embodiments, the invention is directed to a transgenic non-human mammal whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal, and wherein the non-human mammal is a mouse, rat, rabbit, sheep, goat, or pig.

Applicants respectfully submit that the specification provides ample guidance enabling a skilled artisan to make and use the claimed method readily and without undue experimentation. As conceded by the PTO, the specification enables a person skilled in the art to make and use a transgenic scurfy mouse whose cells express a transgene that contains a nucleotide sequence (SEQ ID NO:1) encoding a mouse Fkh^{sf} polypeptide (SEQ ID NO:2), wherein the expression of an *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mouse (*e.g.*, page 33, lines 10-27; page 37, line 15 through page 38, line 5). Therefore, transgenic *Fkh*^{sf} mice may be prepared by introducing a nucleic acid molecule expressing a Fkh^{sf} polypeptide into embryos, implanting the embryos into founder animals, and then breeding the animals according to methods described in the specification (*e.g.*, page 19, line 29 through page 20, line 17, and references cited therein; page 33, lines 10-17) and known in the art. Accordingly, a transgenic *Fkh*^{sf} mouse as encompassed by the amended claims submitted herewith is enabled in compliance with 35 U.S.C. § 112, first paragraph.

Applicants respectfully disagree with the assertion in the Action that undue experimentation would be required for making any and all non-human *Fkh*^{sf} transgenic mammals. By using the disclosed nucleotide sequences, SEQ ID NO:1 that encodes a (murine) Fkh^{sf} polypeptide (SEQ ID NO:2) or SEQ ID NO:3 that encodes a (human) FKH^{sf} polypeptide (SEQ ID NO:4), a person skilled in the art, given the teachings of the instant specification, can make a vector comprising such nucleotide sequences to introduce into pronuclei of fertilized

eggs of a non-human mammal (*see, e.g.*, page 19, line 29 through page 20, line 17, and references cited therein). Applicants submit that at the time the instant application was filed, methods were known in the art for making transgenic mammals other than transgenic mice (*see* Hammer et al., *Nature* 315:680-83 (1985) (describing production of transgenic rabbits, sheep, and pigs), (for instance, as cited in the specification, page 20, line 5; *see also, e.g.*, Markkula and Huhtaniemi, *Reviews of Reproduction* 1:97-106 (1996), page 97, first column). Also, and by way of example, methods were known in the art for making transgenic rabbits that overexpressed human hepatic lipase and ApoE (Barbagallo et al., *Arterioscler. Thromb. Vasc. Biol.* 12:625-32 (1999)); for making transgenic sheep expressing mouse polypeptides (*see, e.g.*, Damak et al., *Biotechnology* 14:181-84 (1996); Damak et al., *Biotechnology* 14:185-88 (1996)); and for making transgenic pigs that expressed normal human hemoglobin (*see, e.g.*, Manjula et al., *Protein Eng.* 11:583-88 (1998)) and that expressed an ovine fusion protein (*see, e.g.*, Pursel et al., *J. Anim. Sci.* 75:2208-14 (1997)). In addition, methods were known in the art at the time the present application was filed for making transgenic goats that expressed biologically active molecules that altered the phenotype of the transgenic goat (*see, e.g.*, Amoah et al., *J. Anim. Sci.* 75:578-85 (1997)). Methods were also known for making transgenic rats that expressed murine polypeptides (*see, e.g.*, Peters et al., *Horm. Metab. Res.* 30:350-54 (1998); Wagner et al., *Pediatr. Nephrol.* 10:108-12 (1996)) or human polypeptides (Taurog et al., *Clin. Rheumatol.* 15 Suppl 1:22-27 (1996)). Applicants submit that the instant specification enables the claimed invention even if some experimentation is required. *See In re Vaeck*, 947 F.2d 488, 495, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991) ("That some experimentation is required is not fatal" to showing that the specification enables the claimed invention.). *See also Ex parte Chen*, 61 U.S.P.Q. 2d 1025, 1028 (Bd. Pat. App. & Interfer. 2000) (finding that even though a success rate for an experimental procedure making a transgenic carp was 1%, the amount of experimentation was not undue).

Accordingly, Applicants submit that the present specification fully enables the skilled artisan to make and use the claimed invention readily and without undue experimentation. Applicants therefore respectfully submit that the present Application satisfies all the requirements of 35 U.S.C. § 112, first paragraph, and request that the rejection be withdrawn.

REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

Claim 40 stands rejected under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. In particular, the Action asserts that the claim, which recites "a reduction of T-Lymphocytes," is unclear as to whether the reduction is in the size of the lymphocytes or the number of lymphocytes.

Applicants respectfully traverse this ground for rejection and submit that the present specification clearly defines that in the claimed transgenic mouse, the expression of the *Fkh*^{sf} transgene results in a decrease in the number of lymphoid cells in a lymph node (*e.g.*, Figure 7; page 37, line 15 through page 38, line 5). Nevertheless, solely to expedite prosecution, Applicants have amended claim 40 to recite a "reduction in number of lymphoid cells in a lymph node." *See, e.g.*, specification, page 37, lines 19-24.

Accordingly, Applicants respectfully submit that the present claim particularly points out and distinctly claims the subject matter which Applicants regard as the invention. Applicants therefore submit that claim 40 fulfills the requirements of 35 U.S.C. § 112, second paragraph, and respectfully request that this rejection be withdrawn.

All claims remaining in the Application are now allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

Mary E. Brunkow et al.

SEED Intellectual Property Law Group PLLC

Mae Joanne Rosok
Registration No. 48,903

MJR:sd

Enclosure:
Postcard

701 Fifth Avenue, Suite 6300
Seattle, Washington 98104-7092
Phone: (206) 622-4900
Fax: (206) 682-6031

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The paragraph beginning at page 5, line 9, of has been twice amended as follows:

Figure 3 depicts a nucleotide sequence of ~~1735~~ 1869 bp corresponding to human *FKHsf* cDNA (SEQ ID NO:3; including a 1293 bp coding region); translation is predicted to initiate at position ~~55~~ 189 and terminate at position ~~1348~~1482.

The paragraph beginning at page 24, line 10, has been amended as follows:

Antibodies which modulate the immune system may readily be prepared given the disclosure provided herein. Within the context of the present invention, antibodies are understood to include monoclonal antibodies, polyclonal antibodies, anti-idiotypic antibodies, antibody fragments (*e.g.*, Fab, and $F(ab')_2$, F_V variable regions, or complementarity determining regions). As discussed above, antibodies are understood to be specific against Fkh^{sf} if they bind with a K_a of greater than or equal to 10^7-M^{-1}, preferably greater than of equal to 10^8-M^{-1}. The affinity of a monoclonal antibody or binding partner, as well as inhibition of binding, can be readily determined by one of ordinary skill in the art (*see* Scatchard, *Ann. N.Y. Acad. Sci. 51*:660-672, 1949).

The paragraph beginning at page 34, line 24, of has been amended as follows:

Figure ~~4~~ 3 shows the nucleotide sequence of the 1869 bp cDNA obtained to date (including an 1293 bp coding region); translation is predicted to initiate at position 189 and terminate at position 1482. Figure 4 shows the sequence of the 431 amino acid human FKH^{sf} protein. Comparison of the predicted coding region of the human gene to the mouse cDNA sequence reveals nearly identical exon structure and 86.1% amino acid sequence identity across the entire protein.

In the Claims:

Claims 34-42 have been amended and new claims 43-45 have been added as follows:

34. (Twice Amended) A transgenic non-human mammal whose cells express an *Fkh*^{sf} transgene ~~that contains a sequence~~comprising a nucleic acid molecule -encoding ~~Fkh~~^{sf} ~~protein~~a polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal, and wherein the mammal is a mouse, rat, rabbit, sheep, goat, or pig.

35. (Amended) A transgenic mouse whose cells express an ~~exogenous~~ *Fkh*^{sf} transgene ~~that contains a sequence~~ comprising a nucleic acid molecule encoding ~~Fkh~~^{sf} ~~protein~~ a polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mouse.

36. (Amended) ~~The~~ A transgenic mouse ~~of claim 35~~, whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:1, wherein the expression of said ~~exogenous~~ *Fkh*^{sf} -transgene results in reduction of T-Lymphocyte proliferation in said mouse.

37. (Amended) The transgenic mouse of either claim 35 or claim 36, wherein the expression of said ~~exogenous~~ *Fkh*^{sf} -transgene results in normal size of said mouse.

38. (Amended) The transgenic mouse of either claim 35 or claim 36, wherein the expression of said ~~exogenous~~ *Fkh*^{sf}- transgene results in normal weight of said mouse.

39. (Amended) The transgenic mouse of either claim 35 or claim 36, wherein the expression of said ~~exogenous~~ *Fkh*^{sf} –transgene results in normal skin appearance of said mouse.

40. (Amended) The transgenic mouse of either claim 35 or claim 36, wherein the expression of said ~~exogenous~~ *Fkh*^{sf} ~~-~~ transgene results in a reduction ~~of T-Lymphocytes~~in number of lymphoid cells in a lymph node.

41. (Amended) The transgenic mouse of either claim 35 or claim 36, wherein the expression of said ~~exogenous~~ *Fkh*^{sf} –transgene results in reduction in T-Lymphocyte responsiveness to cytokines.

42. (Amended) The transgenic mouse of either claim 35 or claim 36, wherein the expression of said ~~exogenous~~ *Fkh*^{sf} –transgene results in reduction in T-Lymphocyte ~~sensitivity~~ responsiveness to stimulation through cell surface receptors.

43. (New) A transgenic non-human mammal whose cells express a *Fkh*^{sf} transgene comprising a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:1, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal, and wherein the mammal is a mouse, rat, rabbit, sheep, goat, or pig.

44. (New) A transgenic mouse whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule selected from the group consisting of (i) a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:4 and (ii) a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:3, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mouse.

45. (New) A transgenic non-human mammal whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule selected from the group consisting of (i) a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:4 and (ii) a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:3, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal, and wherein the mammal is a mouse, rat, rabbit, sheep, goat, or pig.

APPENDIX

CURRENTLY PENDING CLAIMS

At the Examiner's request and for the Examiner's convenience, all currently pending claims, pending entry of the present Amendments, are provided.

34. (Twice Amended) A transgenic non-human mammal whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal, and wherein the mammal is a mouse, rat, rabbit, sheep, goat, or pig.

35. (Amended) A transgenic mouse whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mouse.

36. (Amended) A transgenic mouse, whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:1, wherein the expression of said *Fkh*^{sf} transgene results in reduction of T-Lymphocyte proliferation in said mouse.

37. (Amended) The transgenic mouse of either claim 35 or claim 36, wherein the expression of said *Fkh*^{sf} transgene results in normal size of said mouse.

38. (Amended) The transgenic mouse of either claim 35 or claim 36, wherein the expression of said *Fkh*^{sf} transgene results in normal weight of said mouse.

39. (Amended) The transgenic mouse of either claim 35 or claim 36, wherein the expression of said *Fkh*^{sf} transgene results in normal skin appearance of said mouse.

40. (Amended) The transgenic mouse of either claim 35 or claim 36, wherein the expression of said *Fkh*^{sf} transgene results in a reduction in number of lymphoid cells in a lymph node.

41. (Amended) The transgenic mouse of either claim 35 or claim 36, wherein the expression of said *Fkh*^{sf} transgene results in reduction in T-Lymphocyte responsiveness to cytokines.

42. (Amended) The transgenic mouse of either claim 35 or claim 36, wherein the expression of said *Fkh*^{sf} transgene results in reduction in T-Lymphocyte responsiveness to stimulation through cell surface receptors.

43. (New) A transgenic non-human mammal whose cells express a *Fkh*^{sf} transgene comprising a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:1, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal, and wherein the mammal is a mouse, rat, rabbit, sheep, goat, or pig.

44. (New) A transgenic mouse whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule selected from the group consisting of (i) a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:4 and (ii) a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:3, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mouse.

45. (New) A transgenic non-human mammal whose cells express an *Fkh*^{sf} transgene comprising a nucleic acid molecule selected from the group consisting of (i) a nucleic acid molecule encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:4 and (ii) a nucleic acid molecule comprising a sequence at least 90% identical to the coding region of SEQ ID NO:3, wherein expression of the *Fkh*^{sf} transgene results in reduction of T-lymphocyte proliferation in the mammal, and wherein the mammal is a mouse, rat, rabbit, sheep, goat, or pig.